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Olfaction and Early Detection of Parkinson's Disease

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The article by Ponsen and colleagues[1] and the accompanying editorial by Stern[2] point out the importance of preclinical detection of risk for subsequent development of Parkinson's disease. The interesting work by Ponsen and colleagues[1] would suggest that tests of olfactory function, alone or in combination with other tests, may play a role in developing prognosticating tests. We developed such a test that, when applied prospectively to 212 subjects with symptoms suggestive but not diagnostic of Parkinson's disease, was able to detect 40 of the 59 subjects subsequently diagnosed with Parkinson's disease over a 2-year period.[3,4] Also, the test battery, using tests of olfaction, motor speed, and depression, was able to predict 37 of 40 subjects in whom Parkinson's disease subsequently was clinically excluded. The test battery was 92% specific and 68% sensitive with an area of the receiver operator characteristics curve of 0.88. Olfactory testing alone had a sensitivity of 82% and a specificity of 81%.

Developing any diagnostic or prognostic test is complicated. In addition to specificity and sensitivity, prior probabilities (prevalence of those at risk) are a major factor. For example, the prevalence of persons at risk for Parkinson's disease in a population of concern (such as first-degree relatives or those with specific environmental exposures) would have to be nearly 18% for olfactory testing to have a 50% positive and negative predictive value. Even at this, there would be as many false-positives and false-negatives as true-positives and true-negatives. Often little attention is given to the anticipated prevalence rates of those at risk when discussing potential diagnostic or predictive tests. Combining multiple tests into a diagnostic or prognostic battery to improve specificity and sensitivity is problematic.[3]

Ultimately, the choice of diagnostic or predictive test is social, that is, what are the social, economic, political, moral, and ethical consequences of failing to treat someone at risk versus treating someone not at risk. If an effective neuroprotective therapy is developed, who would be treated? What would happen if an effective neuroprotective treatment cost $10,000 per year and had to be taken continuously? Could or would our society be willing to pay such a cost? Could or would we say that only those who could afford neuroprotection are entitled to it? Perhaps it would be wise to devote efforts to resolve these questions at the same time we are developing neuroprotective therapies.

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Reply

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We are pleased with the interest in our study expressed by Montgomery. He and his colleagues have developed a so-called Parkinson's disease (PD) test battery that includes a single test of olfactory function, from a sample of controls and PD patients in Hoehn and Yahr stages 2 and 2.5.[1] The test was applied subsequently to an independent sample of individuals that is rather vaguely described as having "some concern about the possibility of having PD," "some problem recorded on a questionnaire with high sensitivity and specificity for parkinsonism," and "some symptoms referable to PD."[2] This sample is referred to by Montgomery and colleagues as an enriched sample, chosen to increase the prevalence of participants that subsequently would develop clinically diagnosable PD. However, this actually means that participants were both subjectively and objectively showing motor signs potentially indicative of PD. In contrast, the population we studied to determine whether hyposmia would antedate the development of clinical motor symptoms in PD was both subjectively and objectively (United Parkinson's Disease Rating Scale motor subscores <5) asymptomatic as far as motor signs of PD are concerned.[3,4] Instead, we chose to increase the prevalence of individuals that might later develop PD by selecting first-degree relatives of PD patients (but not cases of familial forms of parkinsonism). Interestingly, Montgomery and colleagues actually applied the PD test battery to a similar sample of asymptomatic first-degree relatives of PD patients in an earlier study[5] referred to in our present and a previous publication.[3,4] Although they found an abnormal score on the PD test battery in 22.5% of first-degree relatives (and in 9% of normal controls), follow-up data so far have not been published. The results of our ongoing prospective study constitute the first evidence that unexplained olfactory dysfunction indeed can precede motor impairments in PD and is associated with an increased risk of PD subsequently developing in first-degree relatives.[4]

We agree with Montgomery that the development of any diagnostic test is fraught with difficulties. The same holds for combining multiple tests into a diagnostic battery. Nevertheless, we should not refrain from trying. Considering that olfactory loss occurs in many other conditions, including Alzheimer's disease, a combination with other tests may be unavoidable when developing a screening test for PD. Although our data suggest that adding single-photon emission computed tomography (SPECT) scanning with a dopamine transporter ligand would appear to be a promising approach, we consider the number of individuals that would need to be

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scanned still too high for practical purposes. The first screening step before SPECT scanning probably should already include multiple modalities. This is what we are currently exploring the same cohort of first-degree relatives.

In the end, many factors come into play when considering the actual implementation of a test battery for a neurodegenerative disorder. The first condition to fulfill is obviously the development of an effective neuroprotective treatment strategy. In balancing the costs of a neuroprotective treatment against the benefits of this treatment, we should also consider the current mean total annual costs of PD patients that are as high as €13,800.[6] At more advanced stages, when hospitalization becomes necessary, there is a substantial further increase in costs up to an annual €29,000.[7]

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Oligodendrocyte Apoptosis before Immune Attack in Multiple Sclerosis?

Michael P. Pender, MD, PhD

Barnett and Prineas[1] recently reported new morphological findings in the brain of a 14-year-old patient with relapsing-remitting multiple sclerosis (MS) who died within 24 hours of the onset of a new symptomatic and fatal brainstem lesion. Within this early lesion, they observed extensive oligodendrocyte cell death which they attributed to apoptosis. Strikingly, no T lymphocytes were detected in the region of oligodendrocyte death. In an accompanying editorial, Trapp[2] suggests that this finding indicates that the immune response in MS is not the cause of the oligodendrocyte cell death but is secondary to oligodendrocyte death caused by an unknown primary disease mechanism. Before accepting this interpretation, two points need to be considered. First, the patient reported by Barnett and Prineas received an intravenous injection of 100mg hydrocortisone.[1] Corticosteroid administration reduces the number of T lymphocytes in the central nervous system in rats with experimental autoimmune encephalomyelitis (EAE).[3] This commences as early as 4 hours after subcutaneous corticosteroid administration.[3] A dose of 0.25mg dexamethasone/kg (equivalent to 6.7mg hydrocortisone/kg) inhibits the development of EAE by an effect on lymphocyte migration rather than by inducing T-lymphocyte apoptosis.[4] Assuming a body weight of 50kg for the patient reported by Barnett and Prineas, the dose of hydrocortisone administered was 2mg/kg, which might have been sufficient to clear T lymphocytes from the central nervous system after these cells had induced oligodendrocyte death. Second, even in the absence of T lymphocytes, antioligodendrocyte antibody can induce oligodendrocyte death and consequent demyelination in the absence of complement and macrophages.[5] Such a mechanism also needs to be considered in MS.

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Reply

John W. Prineas, MB, BS, and Michael H. Barnett, MB, BS

Our study[1] referred to by Professor Pender describes a very early stage in the formation of new multiple sclerosis (MS) lesions characterized by the presence of broad areas of palely staining (but still largely intact) myelin sheaths, containing apoptotic oligodendrocytes and activated microglia, but few or no myelin phagocytes or lymphocytes. The absence of T

lymphocytes in the immediate vicinity of apoptotic oligodendrocytes is especially significant, because such changes have not been reported in any form of the animal model, experimental allergic encephalomyelitis (EAE). As noted by ourselves and Dr Trapp,[2] this raises the possibility of important differences in the pathogenesis of these two diseases. Professor Pender suggests that steroid administration shortly before death may have cleared the central nervous system (CNS) of T cells; this possibility can be ruled out first by the fact that not all seven patients (in whom apoptotic lesions were identified) received such treatment, and second by the presence of numerous lymphocytes in zones of active phagocytosis adjacent to or contiguous with areas exhibiting prominent oligodendrocyte apoptosis in each of the 10 apoptotic lesions described.

In the patient with the 17-hour symptomatic lesion, we described an absence of lymphocytes in zones of oligodendrocyte apoptosis, but relatively numerous CD4, CD8, and especially CD45RO+ T cells together with myelin phagocytes elsewhere in the lesion.[1] Also as noted in our study, the findings were consistent in each of the nine other apoptotic lesions described.

Our findings argue strongly against direct T-cell–mediated destruction of oligodendrocytes in early MS lesions. Rather, they suggest that dissolution of myelin by macrophages is largely or entirely scavenging activity directed against dead myelin sheaths, that is, plasma membrane of apoptotic oligodendrocytes. As noted by Professor Pender, however, our results do not rule out antibody or other humoral factors as effectors of oligodendrocyte apoptosis in early MS lesions.

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